

Daptomycin: a novel lipopeptide antibiotic against Gram-positive pathogens

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Abstract: The aim of this review is to summarize the historical background of drug resistance of Gram-positive pathogens as well as to describe in detail the novel lipopeptide antibiotic daptomycin. Pharmacological and pharmacokinetic aspects are reviewed and the current clinical use of daptomycin is presented. Daptomycin seems to be a reliable drug in the treatment of complicated skin and skin structure infections, infective right-sided endocarditis, and bacteremia caused by Gram-positive agents. Its unique mechanism of action and its low resistance profile, together with its rapid bactericidal action make it a favorable alternative to vancomycin in multi-drug resistant cocci. The role of daptomycin in the treatment of prosthetic material infections, osteomyelitis, and urogenital infections needs to be evaluated in randomized clinical trials.

Keywords: daptomycin, multi-drug resistance, methicillin-resistant *Staphylococcus aureus* (MRSA), pneumonia, urinary tract infection, left-sided endocarditis

Introduction

Gram-positive pathogens have been a challenge to physicians throughout the history of medicine. Multi-drug resistance is an emerging threat in the treatment of in- and outpatient infections caused by staphylococci, streptococci and enterococci.¹ Growing interest in safe and effective antibiotics for the treatment of infections related to resistant Gram-positive bacteria has led to the development and marketing of new substances in recent years, eg, linezolid, tigecyclin, quinupristin-dalfopristin, retapamulin, and daptomycin. This last drug, a lipopeptide antibiotic, has already been successfully used in the on- and off-label treatment of severe Gram-positive bacterial infections including multi-drug resistant pathogens. Daptomycin, the first-in-class cyclic lipopeptide antibiotic, was approved in Europe for the treatment of complicated skin and soft tissue infections in 2006 and for the treatment of right-sided infective endocarditis due to *Staphylococcus aureus* and *S. aureus* bacteremia in 2007.²

The aim of this review is to summarize daptomycin's unique pharmacological and pharmacokinetic properties, its clinical application, and its significance for the treatment of multi-drug resistant pathogens. Detailed information about experimental data on microbiological and pharmacological aspects is beyond the scope of this review, but may be easily found elsewhere.³

History of drugs and drug-resistance in the treatment of Gram-positive microbes

The clinical discovery and early development of penicillin (1928–1940) was a breakthrough in the treatment of a number of serious infections (ie, complicated skin and

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skin-structure infections (cSSSIs), pneumonia, and others).⁴ The first penicillin-resistant cocci were found already in 1944 and the mechanism of penicillinases was detected.⁵ In 1956 methicillin was introduced into clinical practice and only two years later the first methicillin-resistant strain of *S. aureus* (MRSA) had been isolated.⁶ Since then, the prevalence of MRSA and methicillin-resistant *Staphylococcus epidermidis* has steadily increased. In a recent study from the US including 422 emergency department patients, 59% of *S. aureus* isolates from skin and soft tissue infections were resistant to methicillin, with variations from 20% to 72%.⁷

The prevalence of community acquired-MRSA is not uniform in Europe. It ranges from low in France (3.6% of MRSA) and in England, and Wales^{8,9} to high in Greece, with 75% of MRSA strains in the community.¹⁰ The prevalence is also high in Algeria, with 72% of the isolates being MRSA.¹¹ Whereas in 1995 less than 40% of all infections in North-American intensive care units (ICU) were due to MRSA, it was more than 60% in 2004.¹² In the same year 22.6% of all isolates of *S. aureus* in Germany were MRSA.

Vancomycin, a tricyclic glycopeptide produced by *Streptomyces orientalis*, was discovered in 1956 and has been the drug of choice for decades in the treatment of patients with MRSA infections.¹³ Vancomycin is an antibiotic with a number of limitations, beginning with limited levels in many kinds of tissue and numerous side-effects, like nephro- and ototoxicity. Rapid infusion (<10 min) may lead to the “red-man-syndrome”, by liberation of huge amounts of histamine.¹⁴ Furthermore, Von Drygalski et al found vancomycin to be able to cause immune thrombocytopenia by induction of auto-antibodies.¹⁵ Correct dosage of vancomycin is difficult and many authors recommend drug monitoring. Recent data seem to show that continuous infusion of vancomycin may be the best mode of application in patients suffering from acute renal failure, requiring hemofiltration in an ICU setting.^{16–18} The minimum inhibitory concentration of vancomycin has risen in the last decade and consequently the susceptibility break points have been lowered.¹⁹ In 1996 the first vancomycin (glycopeptides) intermediate susceptible *S. aureus* (VISA) (interchangeably GISA) was described and in the first vancomycin-resistant *S. aureus* (VRSA) was detected.²⁰ Since the use of vancomycin has steadily increased in the following decades,²¹ the necessity towards newer antibiotics with bactericidal effects upon these pathogens and a more favorable profile of side effects has grown.

Linezolid is the first marketed antibiotic of the oxazolidinone class with demonstrated activity against antibiotic-susceptible and antibiotic-resistant aerobic Gram-positive cocci, including MRSA, methicillin-resistant coagulase-negative staphylococci, VRSA, and vancomycin-resistant enterococci. Development of linezolid was an important addition to the armamentarium of infectious disease specialists in response to the increasing prevalence of multiple drug-resistant (MDR) Gram-positive pathogens. The possibility of oral administration is a further advantage of linezolid. However, some known side effects, eg, bone marrow depression, limit the use of linezolid to high-risk patients, eg, after solid organ transplantation.

In this context, the *in vitro* data on drug resistance for daptomycin are promising. Silverman et al found a spontaneous rate of resistance for *S. aureus* of <10⁻¹⁰, and for *S. epidermidis*, *Enterococcus faecalis*, *Enterococcus faecium* and *Streptococcus pneumoniae* of <10⁻⁹.²² Since its use in the clinical practice in 2003, more than 120,000 patients have received daptomycin and there have been about 13 cases documented in which resistances could be identified.²³ In cases of reduced susceptibility, combination with other antimicrobial drugs (ie, gentamycin or rifampicin) may be advantageous.²⁴ In most of these the focus of infection could not be eradicated.

Chemical and historical aspects of daptomycin

Daptomycin (LY 146032) is a cyclic lipopeptide, derived from a fermentation product of *Streptomyces roseoporus*. It consists of a 13-member amino acid cyclic lipopeptide (hydrophilic core) with a decanoyl side chain (lipophilic tail).

The drug was first discovered in the 1980s. The initial trials dealt with a dose of 4 mg twice daily and had to be stopped in 1991 because of frequent elevations of serum levels of creatine kinase (CK) probably related to skeletal muscle toxicity.²⁵ In 1999 the drug was re-introduced into clinical trials. The FDA approved daptomycin for the treatment of cSSSIs at a dose of 4 mg/kg daily (preceded by a starting dose of 6 mg/kg/day) at last in 2003.^{26,27} In 2006 an additional FDA approval was granted for the treatment of bloodstream infections and right-sided endocarditis caused by methicillin-sensitive *S. aureus* (MSSA) and MRSA. The approval was confirmed in Europe in 2007.

Antibacterial properties and pharmacological profile of daptomycin

The bactericidal mechanism of daptomycin may be divided into two parts. First of all, the lipophilic decanoyl side

chain is irreversibly bound and then calcium-dependently inserted into the bacterial cell wall without entering the cell's cytoplasm.²⁸ This binding leads to a second reaction consisting of a disruption of the cell membrane, followed by a rapid potassium efflux with subsequent loss of the ion concentration gradient, depolarization of the cell membrane, and a subsequent disruption of the production of macromolecules like RNA, DNA and other proteins.^{29,30} Daptomycin exerts its bactericidal action in a rapid (<60 min) and concentration dependent way. The area under the concentration-time curve is 747 $\mu\text{g}/\text{h}/\text{mL}$ at 6 mg/kg and 494 $\mu\text{g}/\text{h}/\text{mL}$ at 4 mg/kg dosage IV. The maximal plasma concentration (C_{max}) is 98.9 $\mu\text{g}/\text{mL}$ and 57.8 $\mu\text{g}/\text{mL}$, respectively.³¹ A post-antibiotic effect, as known for fluoroquinolones, has also been described for daptomycin: dependent on the calcium concentration, this effect may last for 0.5 to 6.8 hours in staphylococci, enterococci and streptococci, as documented in the literature.^{32,33} The serum half-life of daptomycin is 8.6 hours at 4 mg/kg/day and 8.1 hours at 6 mg/kg/day. It is highly protein-bound (91%–96%) which in combination with its inability to cross cell membranes results in a low volume of distribution (0.09 l/kg).^{34,35} Daptomycin is a large molecule and therefore cannot pass through the gastrointestinal mucosa. Thus, the enteral application is not available. This property of daptomycin is a hindrance in terms of clinical application. However, this property may limit the non-controlled use of daptomycin in the outpatient setting, reducing therefore the risks of developing resistance. Daptomycin is excreted mainly unchanged in the urine (60%) and therefore the dosing interval has to be increased to 48 hours in patients with a creatinine clearance below 30 mL/min.³⁶ Daptomycin also shows efficacy against Gram-positive pathogens, including multi-drug resistant staphylococci, enterococci, and even VISA and vancomycin-resistant enterococcus (VRE) *in vitro*.

Side effects and safety profile of daptomycin

Safety aspects and tolerability have been documented in a number of trials. However, many of the observed potential side effects (AEs) were not clearly attributable to the study medication. The most frequently experienced AEs were gastrointestinal disturbances (ie, constipation, nausea and vomiting and diarrhea), reactions at the injection sites and headache. All these effects were observed in frequencies similar to the comparator drugs (ie, 3%–6%). Musculoskeletal side effects (ie, rise in CK) were the cause for termination of the initial studies on daptomycin in 1985. Interestingly, this effect is probably due to micro-

scopic degenerations and regenerations of muscle fibers. However, as this process does not result in cell lysis and is firstly related to the dosing interval, but not to the plasma levels of daptomycin or drug accumulation,³⁷ it does not seem to be relevant. Of the patients in the daptomycin group of the trial by Arbeit et al, 2.8% showed elevated levels of CK, all returning to normal within two weeks.³⁸ Although recent reports emphasize the clinical safety of daptomycin, even with doses of more than 6 mg/kg/day,³⁹ severe rhabdomyolysis may even occur with current dosing regimens.⁴⁰ In the endocarditis/bacteremia trial, 6.7% of the patients in the daptomycin group showed elevated levels of CK, which were significantly higher than in the comparator group ($P = 0.04$).⁴¹

In the same trial, 9.2% of the patients who received daptomycin developed peripheral neurological symptoms (ie, paresthesias and dysesthesias) which were significantly more common than in the comparator group (1.7%). However, all symptoms were classified as mild to moderate in severity and most were short-lived and completely reversible despite continued treatment.

Clinical applications of daptomycin Daptomycin for CSSSIs

Daptomycin received FDA approval for CSSSIs in 2003 on the basis of two randomized evaluator-blinded phase III studies, comparing daptomycin (4 mg/kg/day) either to vancomycin (1 g/12 h) or an oxacillin class antibiotic (flucloxacillin, cloxacillin, oxacillin or nafcillin at a dose of 4 to 12 mg/kg/day).^{27,42,43} Some interesting details may be mentioned: In both groups (daptomycin and comparator group) about 10% (10% and 9.3%) had infections due to MRSA, with *S. aureus* being the leading cause of infection in the whole study population. Daptomycin was shown to be safe (no higher incidence of side effects) and effective with respect to the kind of infecting agents and the site of infection. Furthermore, retrospective data reported in the CORE study support the effectiveness and safety of daptomycin in the treatment of cSSSI.⁴⁴

Daptomycin for right-sided endocarditis and bacteremia

In 2006 Fowler et al published a randomized controlled trial which compared daptomycin to vancomycin or anti-staphylococcal penicillins in combination with gentamycin.⁴⁵ On the whole, daptomycin and standard treatment were equally effective at the end of treatment (61% vs 60.9%) and 42 days after the end of treatment (44.2% vs 41.7%).

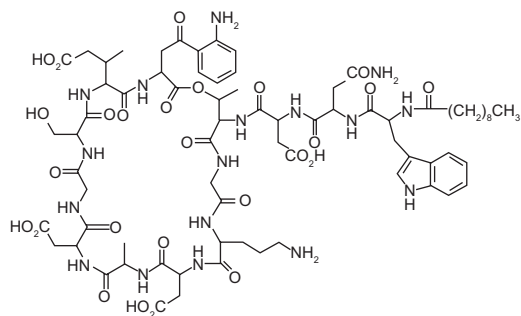


Figure 1 Chemical structure of daptomycin.

Some limitations of the trial may be mentioned. First of all, there were more relapsing infections due to *S. aureus* in the daptomycin group (15.8% vs 9.6%; not statistically significant). Furthermore, the trial cannot give significant information about left-sided endocarditis, as only 18 patients with this disease were included. The success rate in this group was very low in both study groups. In conclusion, daptomycin seems to be a promising alternative to standard therapeutic approaches in patients with right-sided endocarditis and bacteremia.

Off-label use of daptomycin

Bone and joint infections

Daptomycin was found to be a promising option in the therapy of patients presenting with bone and joint infections by Falagas et al. They resumed the clinical use of this lipopeptide antibiotic in patients with bone and joint infections in a systematic review.⁴⁶ In different case reports, including discitis, osteomyelitis, hip and knee infection, septic arthritis, as well as different joint inflammatory processes, daptomycin proved efficient with an initial full remission of the infection of 58%. The decision to switch to daptomycin was taken after failure of the administered monotherapy with vancomycin alone, or in combination with other antibiotics. MRSA was the predominant pathogen (83%) in the cases presented. Some case series^{47–49} documented the safe use of daptomycin in patients ($n = 53$) suffering from bone and joint infections, the principal indication being osteomyelitis. In these patients, MRSA was again the predominant responsible pathogen (73%) and the reported cure of infection after intravenous administration of a standard dose of 4–6 mg/kg/day was 81%. Although the effective use of daptomycin in joint and bone infections documented by Falagas et al⁵⁰ is almost exclusively in orthopedic patients, this report must be kept in mind for decision-making in heart surgery patients presenting with multi-resistant Gram-positive infections of the sternotomy wound, which commonly

originate osteomyelitis and presents almost no other surgical alternative.^{51,52}

The successful treatment of prosthetic material with daptomycin has also been documented in the literature. Antony et al and Carlyn et al reported the use of daptomycin in knee prostheses MRSA infection^{47,53} Furthermore, Cunha et al employed daptomycin successfully in the treatment of different prosthetic material infections, including MRSA infection of a pacemaker⁵⁴ and a MSSA infection of a peripherally inserted central catheter.⁵⁵ Weis et al reported the treatment with daptomycin of a patient presenting with a MRSA infection in a biventricular assist device.⁵⁶ Presterl et al reported recently the use of daptomycin in cardiac device infections with *S. epidermidis*.⁵⁷ Beiras-Fernandez et al documented a case series of 8 patients presenting with ventricular assisted devices successfully treated with daptomycin after multidrug resistant pathogen infection.

Urinary tract infections

Daptomycin presents favorable pharmacokinetics for this kind of infection as 66% of the active drug is excreted in the urine.⁵⁸ Furthermore, *in vitro* data show a good activity of daptomycin in comparison to linezolid and vancomycin for Gram-positive uropathogens causing complicated urinary tract infections. However, these promising results have not yet been confirmed by clinical trials.⁵⁹

Community-acquired pneumonia (CAP)

Daptomycin was ineffective for CAP treatment in two phase III non-inferiority trials (cure rate 79% vs 87%)²⁷ when compared to ceftriaxone. A murine *in vitro* model demonstrated that the pulmonary surfactant acts as a scavenger for daptomycin, leading to high levels in the epithelial lining fluid, but a low insertion rate into the bacterial cell wall.⁶⁰ Daptomycin inserts preferentially into pulmonary surfactant and thus shows a significant elevation of the MIC in lungs with rising concentrations of surfactant. In patients with hematogenous pneumonia the results might be better.

Left-sided endocarditis

Daptomycin has been approved for use in bacteremia and right-sided endocarditis in 2007; however, left-sided endocarditis therapy remains off-label. Different experimental models involving different pathogens such as MRSA, MSSA, *Enterococcus* spp, and VRE for left-sided endocarditis have shown

a very promising antimicrobial activity of daptomycin^{61–64}. Furthermore, Cunha et al and Mergenhagen et al reported successful treatment with 6 mg/kg/day daptomycin of MRSA left-sided endocarditis.⁶⁵ Falagas et al performed a systematic review of the use of daptomycin in patients presenting with endocarditis and included some cases regarding its successful use in left-sided endocarditis.⁶⁶

Although daptomycin proved efficient in some of the above stated indications, further clinical evidence in form of randomized clinical trials is needed to evaluate its effectiveness and safety in osteomyelitis, mediastinitis, joint infection, prosthetic material infections and left-sided endocarditis.

Experimental data on topical application

Despite the very modest extent of side-effects described for daptomycin, experimental use of topical daptomycin has been brought forward in recent years.⁶⁷ Antibiotic-loaded bone-cement seems to be the most promising option in this field. It seems to be possible to provide sufficient peak and sustained concentrations of daptomycin to inhibit bacterial growth even in infected bones.⁶⁸ The clinical relevance of these data will have to be proven by randomized controlled trials.

Conclusions

Development of new antibiotics is essential due to the increasing incidence of antibiotic drug resistance. Daptomycin, a new lipopeptide antibiotic, has proven a successful and less toxic alternative to vancomycin in the treatment of multidrug resistant Gram-positive pathogens. It seems to be a reliable drug in the treatment of cSSSIs, infective right-sided endocarditis, and bacteremia caused by Gram-positive agents. The role of daptomycin in the treatment of prosthetic material infections, mediastinitis, osteomyelitis, and urogenital infections needs to be further evaluated.

Disclosure

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